WARNER LAMBERT CO LLC *EP 1348433-A1

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New thiazol-2-yl-imine compounds useful as phosphodiesterase-7 inhibitors for treating e.g. osteoarthritis, multiple sclerosis, osteoporosis, asthma, cancer and graft rejection (Eng)

C2003-235024 R(AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR)

Addnl. Data: VERGNE F, BERNARDELLI P, LORTHIOIS E, DUCROT P

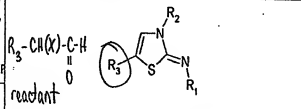
B(7-E1, 14-AZB1, 14-C1, 14-C3, 14-C9A, 14-D7A, 14-E10, 14-E10C, 14-G1B, 14-G2A, 14-G2C, 14-G2D, 14-H1, 14-J1, 14-K1, 14-K1A, 14-N4, 14-N13, 14-S1) .11

NOVELTY

Thiazol-2-yl-imine compounds (I), their racemic forms, isomers, N-oxides, and their acidic or basic salt forms are new.

DETAILED DESCRIPTION

Thiazol-2-yl-imine compounds of formula (I), their racemic forms, isomers, N-oxides, and their acidic or basic salt forms are new;



(I)

R_1 = (hetero)cycloalkyl or (hetero)aryl (all optionally substituted by halogen, trifluoromethyl, nitro, cyano, oxo, $-NR_4R_5$, $-CO_2R_4$, $-CONR_4R_5$, $-OR_4$, $-S(O)_nR_4$, $-S(O)_nR_4R_5$, tetrazolyl or 1-6C alkyl (optionally mono- - tri-substituted by $-OR_4$, $-NR_4R_5$ or $-CO_2R_4$));

n, m = 0-2;

R_4, R_5 = H or $-X_1R_4$;

R_2 = 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, aryl or cycloalkyl;

X_1, X_2 = single bond or 1-6C alkylene;

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R_4 = 1-6C alkyl, (hetero)cycloalkyl or (hetero)aryl;

R_5 = (hetero)cycloalkyl or (hetero)aryl (all optionally substituted by halo, nitro, cyano, trifluoromethyl, oxo, 1-6C alkyl, $-OR_6$, $-NR_6R_7$, $-COR_6$, $-CO_2R_6$, $-CONHOH$, $-CONR_6R_7$, $-S(O)_nR_6$, $-S(O)_nNR_6R_7$, $-NR_6COR_7$, $-NR_6SO_2R_7$, $-N(SO_2R_7)_2$, $-NR_6$-CO-NR_7R_8 or tetrazolyl;

R_6, R_7 = H or $-X_2R_8$;

R_8 = 1-6C alkyl, (hetero)cycloalkyl, or (hetero)aryl (all optionally mono- - tri-substituted by OH, 1-6C alkoxy, 1-6C alkyl, amino, mono-1-6C alkylamino, di-1-6C alkylamino, carboxy, 1-6C alkoxycarbonyl or benzyl;

R_9 = H or 1-6C alkyl.

The aryl is an aromatic monocyclic or bicyclic system containing 5-10C and in the bicyclic ring system, one of the ring is aromatic and the other ring is optionally aromatic or partially hydrogenated and when the second ring is partially hydrogenated, then the ring is optionally mono- or di-substituted by oxo.

The heteroaryl is the aryl group in which 1-4 carbon atoms are replaced by 1-4 heteroatoms selected from O, S or N.

The cycloalkyl is a monocyclic or polycyclic system containing 3-10C and is saturated or partially unsaturated but without aromatic character and in the polycyclic system, each cycle could be fused together or formed a link.

The heterocycloalkyl is the cycloalkyl group in which 1-4 carbon atoms are replaced by 1-4 heteroatoms selected from O, S and N.

An INDEPENDENT CLAIM is included for preparation of (I).

ACTIVITY

Immunosuppressive; Antiinflammatory; Respiratory-Gen.; CNS-Gen.; Antiallergic; Gastrointestinal-Gen.; Analgesic; Osteopathic; Neuroprotective; Antiasthmatic; Cytostatic; Anti-HIV; Antiarthritic.

MECHANISM OF ACTION

Phosphodiesterase-7 (PDE-7) inhibitor.

The compounds (I) were tested to inhibit cyclic nucleotide phosphodiesterase 7 as given in W.J.Thompson et al. 1979, Advances in Cyclic Nucleotide Research, Vol.10:69 - 92, ed. G.Brooker et al. Raven Press, NY and showed IC_{50} valne of 0.02-100 micro M.

No results for specific compounds are given.

USE

(I) Are used for the treatment of a disease (e.g. T-cell related disease, autoimmune disease, inflammatory disease, respiratory

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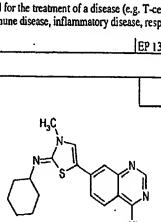
disease, CNS disease, allergic diseases, endocrine or exocrine pancreas disease, gastrointestinal diseases, visceral pain, inflammatory bowel disease, osteoarthritis, multiple sclerosis, osteoporosis, osteoarthritis, multiple sclerosis, chronic obstructive pulmonary disease (COPD), allergic rhinitis, asthma, cancer, acquired immune deficiency syndrome (AIDS) and graft rejection (claimed).

ADVANTAGE

The compounds (I) are selective PDE-7 inhibitors and are active at very low concentrations.

SPECIFIC COMPOUNDS

4 Compounds are specifically claimed as (I), i.e. N-{4-[(2Z)-2-(cyclohexylimino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]phenyl}acetamide, N-[4-[(2Z)-2-[(3-hydroxycyclohexyl)imino]-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]phenyl]acetamide, 7-[(2Z)-2-(cyclohexylamino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]quinazoline-4-amine (Ia) and 7-[(2Z)-2-[(3-hydroxycyclohexyl)imino]-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]quinazoline-4-amine.



(Ia)

ADMINISTRATION

(I) Are administered orally, parenterally (including intravenously, intramuscularly or subcutaneously), per- or trans-cutaneously, intravaginally, rectally, nasally, perlingually, buccally, ocularly or by respiratory route, at a dosage of 1 mg - 1 g per day.

EXAMPLE

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(con't)

A solution of diethyl-(4-oxo-3,4-dihydroquinazolin-2-yl)acetaldehyde and N-cyclohexylthiourea in dimethylformamide was heated at 70 °C for 5-12 hours. The mixture was quenched with 10% dimethylamine in ethanol and the solvent was removed, the crude was purified to obtain 7-[2-(cyclohexylamino)-1,3-thiazol-5-yl]quinazolin-4(3H)-one (A).

To a solution of (A) in anhydrous dioxane, methyltrifluoromethane sulfonate (1.1 equivalents) was added. The resulting mixture was stirred for 24 hours. Triethylamine (2 equivalents) was added, then the mixture was concentrated. The residue was purified to obtain 7-[(2Z)-2-(cyclohexylimino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]quinazoline-4(3H)-one (A1).

A mixture of (A1), thionyl chloride and dimethylformamide, in toluene was refluxed for 3 hours before distillation of solvents under reduced pressure. The residue was diluted in dichloromethane and then neutralized with triethylamine, followed by a work-up to obtain N-(2Z)-5-(4-chloroquinazolin-7-yl)-3-methyl-1,3-thiazol-2(3H)-ylidene]-N-cyclohexylamine (A2).

A solution of (A2) in a 2 N solution of ammonia (NH_3) in isopropanol was stirred for 6 hours at 60 °C.

The mixture was then concentrated. To this residue a solution of sodium hydroxide (NaOH) (0.1 N) was added and then worked up to obtain 7-[(2Z)-2-(cyclohexylimino)-3-methyl-2,3-dihydro-1,3-thiazol-5-yl]quinazolin-4-amine (Ia).

DEFINITIONS

Preferred Definitions:

R_1 = cyclohexyl group (optionally mono-substituted by OH) or phenyl (optionally mono-substituted by tetrazolyl or $-CO_2R_4$);
R_2 = H or 1-6C alkyl;
R_3 = methyl;
R_3 = quinoxalinyl, 1H-quinazolinyl, 3H-quinazolinyl-4-one or 1H-quinazolinyl-2,4-dione (all optionally mono- tri-substituted by halo, 1-6C alkyl, OR_8 or NR_8R_9);
X_2 = single bond;
R_8 = 1-6C alkyl (optionally monosubstituted by OH, 1-6C alkoxy, amino, mono-1-6C alkylamino or di-1-6C alkylamino.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation (claimed): Preparation of (I) involves: (1) reacting an α-haloacetate of formula R_3-CH(X)-C(=O)-H (II) with a thiourea of formula R_2-NH-C(=S)-NH-R_1 (III) in the presence of an inert solvent under heating condition to form a mixture of

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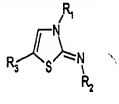
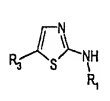
formula (I) and (IV), followed by separation of (I) from the mixture, or reacting (II) with thiourea of compound of formula H_2N-C(=S)-NH-R_1 (V) to give thiazole derivative of formula (VI);
(2) condensing (VI) with R_2-L_1 (VII) to give (I);
(3) purifying (I) by a conventional purifying technique; and
(4) separating into their respective isomers, followed by converting into their salts with acid or base or into N-oxide.



(IV)



(VI)

X = halogen;
L^1 = leaving group.
All other definitions are as above.

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